SEXUAL MEDICINE REVIEWS

The Safety and Efficacy of Growth Hormone Secretagogues

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ABSTRACT

Introduction: Growth hormone (GH) increases lean body mass, decreases fat mass, increases exercise tolerance and maximum oxygen uptake, enhances muscle strength, and improves linear growth. Long-term studies of GH administration offer conflicting results on its safety, which has led to strict Food and Drug Administration criteria for GH use. The potential drawbacks of exogenous GH use are believed to be due in part to impaired regulatory feedback.

Aim: To review the literature on GH secretagogues (GHSs), which include GH-releasing peptides and the orally available small-molecule drug ibutamoren mesylate.

Methods: Review of clinical studies on the safety and efficacy of GHSs in human subjects.

Main Outcome Measure: Report on the physiologic changes from GHS use in human subjects including its safety profile.

Results: GHSs promote pulsatile release of GH that is subject to negative feedback and can prevent supratherapeutic levels of GH and their sequelae. To date, few long-term, rigorously controlled studies have examined the efficacy and safety of GHSs, although GHSs might improve growth velocity in children, stimulate appetite, improve lean mass in wasting states and in obese individuals, decrease bone turnover, increase fat-free mass, and improve sleep. Available studies indicate that GHSs are well tolerated, with some concern for increases in blood glucose because of decreases in insulin sensitivity.

Conclusion: Further work is needed to better understand the long-term impact of GHSs on human anatomy and physiology and more specifically in the context of a diversity of clinical scenarios. Furthermore, the safety of these compounds with long-term use, including evaluation of cancer incidence and mortality, is needed. **Sigalos JT, Pastuszak AW. The Safety and Efficacy of Growth Hormone Secretagogues. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Growth Hormone; Growth Hormone Secretagogue; Growth Hormone Releasing Peptide; Hexarelin; Ibutamoren; Growth Hormone Releasing Peptide-2; Growth Hormone Releasing Peptide-6

INTRODUCTION

Growth hormone (GH), which is produced by somatotroph cells of the anterior pituitary, exhibits pulsatile secretion that promotes linear growth in children by acting on the epiphyseal plates of the long bones.[1] GH also increases lipolysis, stimulates protein synthesis, and antagonizes insulin action.[1] Although GH receptors exist in many organs and are responsible for some direct effects, many peripheral effects of GH are attributed to insulin-like growth factor-1 (IGF-1).[1,2] IGF-1 is regulated by GH binding to a receptor homodimer, located primarily in the liver, which regulates intracellular signaling through a phosphorylation cascade involving the JAK-STAT pathway.[1] Serum IGF-1 levels are a surrogate for GH levels because of the relation of IGF-1 as a downstream effector and upstream regulator of GH and a half-life that is markedly longer than that of GH.[1]

Because of its anabolic effects, the use of recombinant GH has been studied in GH-deficient adults examining different end points, including bone mineral density, exercise tolerance and performance, muscle strength, skin effects, immune function, and quality of life, among others.[3] From these studies, we have learned that exogenous GH can increase lean body mass and decrease fat mass,[4–6] increase exercise tolerance,[7,8] increase maximum oxygen uptake in adults,[9–11] and increase muscle strength and cross-sectional area.[12]

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Table 1. Characteristics of growth hormone secretagogues

Name	Oral availability	Half-life	Benefits	Side effects
DTrp2[25]	No in vivo data; in vitro data only	No in vivo data; in vitro data only	No in vivo activity	No in vivo activity
GHRP-6[66]	0.30%	0.30 h	Restoration of GH secretion in the obese,[52,53] increased time in stage 2 sleep[59]	Transient increase in cortisol[59]
GHRP-2[66,67]	0.30–1.0%	0.52 h	Increase in growth velocity in children,[41,42] increase in appetite,[44,45] weight gain in anorexia,[46] normalization of IGF-1 in critical illness[47]	Transient increase in appetite,[40] transient increase in cortisol[45]
Hexarelin[66,68]	0.20%	0.83 h	Increased growth velocity in children[39]	Shorter stage 4 sleep in first half of night[61]
MK-0751 (L-692,429)[27,66,69]	negligible	4.7 h	Increased GH secretion[37,38]	Flushing and warm sensation,[37,38] transient increase in cortisol and prolactin[38]
Ibutamoren (MK-0677, L-163,191)[27,69]	>60%	4.7 h	Reversal of nitrogen wasting,[48] functional lower extremity improvement post hip fracture,[50,51] increase in FFM[56,58] decreased LDL,[58] longer REM sleep and shorter sleep latency[62]	Transient increase in cortisol and prolactin,[48,56] musculoskeletal pain and fluid retention,[49,50,58] increase in insulin insensitivity,[50,51,56,58,65] transient increase in appetite[58]

FFM = fat-free mass; GH = growth hormone; GHRP = growth hormone releasing peptide; IGF-1 = insulin-like growth factor-1; LDL = low-density lipoprotein cholesterol; REM = rapid eye movement.

Despite these benefits, GH use is restricted by the Food and Drug Administration (FDA) to a discrete set of conditions.[13,14] Current indications for GH therapy in adults include (i) documented GH deficiency in childhood, (ii) documented hypopituitarism as a result of pituitary or hypothalamic disease, surgery, radiation therapy, trauma, or aneurysmal subarachnoid hemorrhage, (iii) AIDS wasting syndrome,[15–17] and (iv) short bowel syndrome. Use of GH for anabolic applications, except in the setting of AIDS where GH has shown efficacy in alleviating lipodystrophy,[15] improving muscle performance,[16] and treating HIV-induced muscle wasting,[17] is not currently approved because of safety concerns.[13] These concerns arose from large European studies that followed children on long-term recombinant GH therapy and observed increased mortality in the cohort.[18] Other studies have linked exogenous GH use and increases in IGF-1 levels with an increased risk of malignancy.[19] Carel et al[18] observed higher mortality rates from bone cancers and cerebral hemorrhage in patients on GH. However, GH supplementation did not correlate with mortality in a dose-dependent manner, with no increase in mortality as a function of GH treatment duration or overall exposure. In contrast, a study using Denmark's nationwide population registry observed lower mortality in children receiving recombinant GH compared with age-matched controls.[20] More generally, complications arising from exogenous GH therapy can result from supra-therapeutic levels of GH and the bypass of regulatory feedback mechanisms.[19,21]

Given the potential risks of exogenous GH use, alternative therapies that avoid these risks would be welcome additions in the management of GH-deficient patients. GH secretagogues (GHSs), which include GH-releasing peptides (GHRPs) and small-molecule drugs that can stimulate secretion of endogenous GH, could provide the benefits of GH and minimize negative sequelae. In this review, we summarize the literature examining the safety and efficacy of GHSs.

HISTORY AND PHYSIOLOGY OF GROWTH HORMONE SECRETAGOGUES

GHRPs were first synthesized by Bowers et al[22] in 1977 as a series of synthetic enkephalin opiate analogues that stimulated GH release from rat pituitary cells in vitro (Table 1). The first peptide that was found to stimulate GH release from rat pituitary cells was Tyr-DTrp^2-Gly-Phe-MetNH_2. This original GHRP mimicked GH-releasing hormone (GHRH), but was found to only weakly stimulate GH secretion in vitro.[23] The first GHRP with significant in vivo activity was a hexapeptide, His-DTrp-Ala-Trp-DPhe-LysNH_2, also known as GHRP-6.[24,25] Despite mimicking natural GHRH action, GHRPs do not bind the seven-transmembrane domain, G-protein–coupled GHRH receptor, which functions through the protein kinase A pathway. Rather, GHSs bind a receptor that is coupled to members of the Gq/i family of proteins and that activates phospholipase C.[24,26] Subsequent work showed that GHRPs did not attenuate